GENERIC PHARMACEUTICAL INDUSTRY ASSOCIATION

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Alice E. Till, Ph.D.
President



November 15, 1999

Food and Drug Administration
Dockets Management Branch (HFA – 305)
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Draft Guidance for Industry on Average, Population, and Individual Approaches to Establishing Bioequivalence [Docket No. 87D-0433]

Dear Sir or Madam:

On behalf of the Science committee of the Generic Pharmaceutical Industry Association (GPIA), I would like to submit brief comments to you on "Draft Guidance for Industry on Average, Population, and Individual Approaches to Establishing Bioequivalence", 64(173) FR, 48842, September 8, 1999. The deadline for comments on this guidance was November 8, 1999. Despite the lateness of our comments, we would appreciate your consideration of them as the draft guidance is finalized. These comments have also been included in our comments on "Draft Guidance for Industry on BA and BE Studies for Orally Administered Drug Products-General Considerations" [Docket No. 99D-2729], submitted to the docket on November 2, 1999.

With respect to the concepts of individual bioequivalence and subject-by-formulation interaction which are addressed in both guidances, we would like to reiterate the following concerns.

Individual bioequivalence (IBE) is not a method accepted by the community of scientists as a valid method of determining the bioequivalence of two products. It is based on a statistical method for bioequivalence that has not been shown to be necessary or statistically robust.

IBE is not a method accepted by the community of scientists as a valid method of determining the bioequivalence of two products. There is an emerging emphasis on the subject-by-formulation interaction as estimated according to this guidance. This is a new representation of the old argument that products shown to be bioequivalent in healthy young men are not necessarily bioequivalent in patients. There have been many efforts to prove this argument and it has not been accomplished. The broad imposition of replicate design studies and the opinion that $\sigma_D \geq 0.15$ is reason for "concern" has no basis in scientific evidence. Two important elements of scientific evidence are rationality and repeatability. This change to establishing bioequivalence has met neither of these basic scientific criteria.

The application of IBE would be premature. The behavior of this statistic for drug products with low variability has not been well described. Therefore, the application of an individual BE criterion (with reference scaling) for drug products with low variability is not an appropriate regulatory recommendation.

Thank you for the opportunity to comment on this very important guidance.

Sincerely,

Alice E. Till, Ph.D.
President

CC E. Lane, Chair GPIA BA/BE Taskforce
M. Chen, FDA

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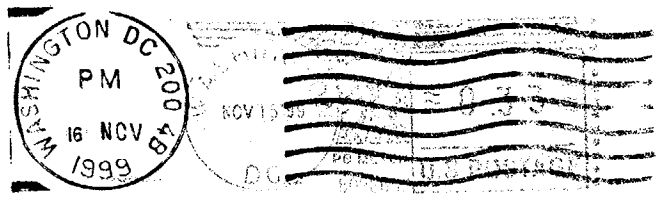


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